

# Speciation, stability constants and structures of complexes of copper(II), nickel(II), silver(I) and mercury(II) with PAMAM dendrimer and related tetraamide ligands

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## Abstract

The acid–base properties and Cu(II), Ni(II), Ag(I) and Hg(II) binding abilities of PAMAM dendrimer, **L**, and of the simple model compounds, the tetraamides of EDTA and PDTA, **L**<sup>1</sup>, were studied in solution by pH-metric methods and by <sup>1</sup>H NMR and UV–Vis spectroscopy. PAMAM is hexabasic and six pK<sub>a</sub> values have been determined and assigned. PAMAM forms five identifiable complexes with copper(II), [CuLH<sub>4</sub>]<sup>6+</sup>, [CuLH<sub>2</sub>]<sup>4+</sup>, [CuLH]<sup>3+</sup>, [CuL]<sup>2+</sup> and [CuLH<sub>-1</sub>]<sup>+</sup> in the pH range 2–11 and three with nickel(II), [NiLH]<sup>3+</sup>, [NiL]<sup>2+</sup> and [NiLH<sub>-1</sub>]<sup>+</sup> in the pH range 7–11. The complex [CuLH<sub>4</sub>]<sup>6+</sup>, which contains two tertiary nitrogen and three amide oxygen atoms coordinated to the metal ion, is less stable than the analogous EDTA and PDTA tetraamide complexes [CuL<sup>1</sup>]<sup>2+</sup>, which contain two tertiary nitrogen and four amide oxygen atoms, due to ring size and charge effects. With increasing pH, [CuLH<sub>4</sub>]<sup>6+</sup> undergoes deprotonation of two coordinated amide groups to give [CuLH<sub>2</sub>]<sup>4+</sup> with a concomitant change from O-amide to N-amidate coordination. Surprisingly and in contrast to the tetraamide complexes [CuL<sup>1</sup>]<sup>2+</sup>, these two deprotonation steps could not be separated. As expected the nickel(II) complexes are less stable than their copper(II) analogues. The tetra-*N*-methylamides of EDTA, **L**<sup>1</sup>(**b**), and PDTA form mononuclear and binuclear complexes with Hg(II). In the case of **L**<sup>1</sup>(**b**) these have stoichiometries HgL<sup>1</sup>(**b**)Cl<sub>2</sub>, [HgL<sup>1</sup>(**b**)H<sub>-2</sub>Cl<sub>2</sub>]<sup>2-</sup>, [Hg<sub>2</sub>L<sup>1</sup>(**b**)Cl<sub>2</sub>]<sup>2+</sup>, Hg<sub>2</sub>L<sup>1</sup>(**b**)H<sub>-2</sub>Cl<sub>2</sub> and [Hg<sub>2</sub>L<sup>1</sup>(**b**)H<sub>-5</sub>Cl<sub>2</sub>]<sup>3-</sup>. Based on <sup>1</sup>H NMR and pH-metric data the proposed structure for HgL<sup>1</sup>(**b**)Cl<sub>2</sub>, the main tetraamide ligand containing species in the pH range <3–6.5, contains **L**<sup>1</sup>(**b**) coordinated to the metal ion through the two tertiary nitrogens and two amide oxygens while the structure of [HgL<sup>1</sup>(**b**)H<sub>-2</sub>Cl<sub>2</sub>]<sup>2-</sup>, the main tetraamide ligand species at pH 7.5–9.0, contains the ligand similarly coordinated but through two amidate nitrogen atoms instead of amide oxygens. The proposed structure of [Hg<sub>2</sub>L<sup>1</sup>(**b**)Cl<sub>2</sub>]<sup>2+</sup>, a minor species at pH 3–6.5, also based on <sup>1</sup>H NMR and pH-metric data, contains each Hg(II) coordinated to a tertiary amino nitrogen, two amide oxygens and a chloride ligand while that of [Hg<sub>2</sub>L<sup>1</sup>(**b**)H<sub>-5</sub>Cl<sub>2</sub>]<sup>3-</sup>, contains each Hg(II) coordinated to a tertiary amino nitrogen, two amidate nitrogens, a chloride and a hydroxo ligand in the case of one of the Hg(II) ions. The parent EDTA and PDTA amides only form mononuclear complexes. PAMAM also forms dinuclear as well as mononuclear complexes with mercury(II) and silver(I). In the pH range 3–11 six complexes with Hg(II) i.e. [HgLH<sub>4</sub>Cl<sub>2</sub>]<sup>4+</sup>, [HgLH<sub>3</sub>Cl<sub>2</sub>]<sup>3+</sup>, [Hg<sub>2</sub>LCl<sub>2</sub>]<sup>2+</sup>, [Hg<sub>2</sub>LH<sub>-1</sub>Cl<sub>2</sub>]<sup>+</sup>, [HgLH<sub>-1</sub>Cl<sub>2</sub>]<sup>-</sup> and [HgLH<sub>-2</sub>Cl<sub>2</sub>]<sup>2-</sup> were identified and only two with Ag(I), [AgLH<sub>3</sub>]<sup>4+</sup> and [Ag<sub>2</sub>L]<sup>2+</sup>. Based on stoichiometries, stability constant comparisons and <sup>1</sup>H NMR data, structures are proposed for these species. Hence [HgLH<sub>4</sub>Cl<sub>2</sub>]<sup>4+</sup> is proposed to have a similar structure to [CuLH<sub>4</sub>]<sup>6+</sup> while [Hg<sub>2</sub>LCl<sub>2</sub>]<sup>2+</sup> has a similar structure to [Hg<sub>2</sub>L<sup>1</sup>(**b**)H<sub>-5</sub>Cl<sub>2</sub>]<sup>3-</sup>. © 2005 Elsevier B.V. All rights reserved.

**Keywords:** Metal ions; PAMAM dendrimer complexes; Speciation; Structures; Potentiometry; NMR

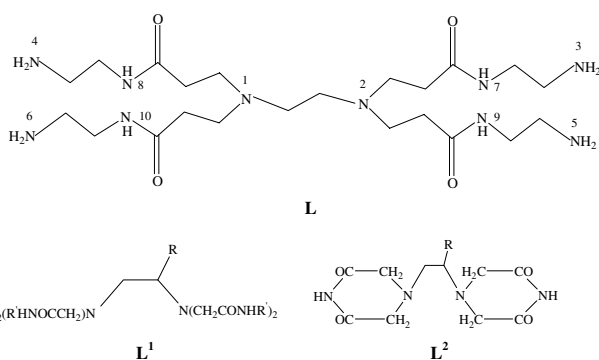
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## 1. Introduction

Polyamidoamine (PAMAM) dendrimers, **L**, are highly branched polymers consisting of an ethylenediamine core as well as interior amide groups and terminal amino groups [1]. They are especially attractive for binding metal ions in aqueous solution due to their controlled size. PAMAM dendrimers are carrier molecules for MRI contrast agents and can be applied in the targeted delivery of drugs as well as transfection vectors in gene therapy [2]. Recently they have been shown to be active against viruses by blocking herpes simplex virus attachment to cells.

PAMAM dendrimers are also high capacity chelating agents for metal ions such as Cu(II), Ni(II) [3] and Pt(II) [4]. In this paper we present speciation results for systems containing PAMAM dendrimer **L** with Cu(II) and Ni(II) as well as the heavy metal ions, Ag(I) and Hg(II). The tetraamides of EDTA and PDTA, **L**<sup>1</sup>, are structurally similar to the simplest PAMAM dendrimers but lack the terminal amine functionalities. These tetraamides are aminolysis products of the diimides **L**<sup>2</sup>, the best known of which is the anticancer drug Razoxane (R = Me) [5]. We also report results of speciation studies for systems containing tetraamides **L**<sup>1</sup>(a)–(d) with Cu(II), Ni(II) and Hg(II) (but not Ag(I) due to insolubility) for comparative purposes.



- (a) R = R' = H; (b) R = H, R' = Me  
(c) R = Me, R' = H (d) R = R' = Me

## 2. Experimental

### 2.1. Materials

PAMAM dendrimer **L** was purchased from Aldrich as a 20% methanol solution. The tetraamides **L**<sup>1</sup>(a)–(d) were synthesized according to literature methods [6]. D<sub>2</sub>O (99.9%) and NaOD (40% in D<sub>2</sub>O) were purchased from Cambridge Isotope Laboratories, Inc.

### 2.2. Potentiometric measurements

pH-metric titrations were carried out at 25 ± 0.1 °C using solutions of 0.2 mol dm<sup>-3</sup> ionic strength (KCl for Cu(II) and Ni(II) and KNO<sub>3</sub> for heavy metal ions) under a nitrogen atmosphere. Carbonate-free KOH solutions of known concentrations (ca. 0.2 mol·dm<sup>-3</sup>) standardized with potassium hydrogen phthalate [7], were used as titrant. The pH-metric studies were carried out on a Mettler DL25 automatic titrator fitted with a Mettler DG III combined electrode and on a Molspin pH meter and titration controller with Thermo Russell CMAW711 combined electrode and Hamilton syringe autoburette. The electrode system was calibrated daily by the method of Irving et al. [8] (pK<sub>w</sub> = 13.831) and the pH-meter readings were converted into hydrogen ion concentrations.

The pK<sub>a</sub> values of PAMAM, **L** and of the EDTA and PDTA tetraamides **L**<sup>1</sup> were determined by titrating solutions (~1.0 × 10<sup>-3</sup> and ~2.0 × 10<sup>-3</sup> mol·dm<sup>-3</sup>) in HCl or HNO<sub>3</sub> (~5.0 × 10<sup>-3</sup> mol·dm<sup>-3</sup> and ~10.0 × 10<sup>-3</sup>) over the pH range 2.2–10.5 with a KOH solution of known concentration (0.1985 mol·dm<sup>-3</sup>). This method was also used to determine the exact concentrations of the ligands. The resulting data were analyzed using the SUPERQUAD [9] and HYPERQUAD 2000 [10] computer programs. Stability constants of the Cu<sup>2+</sup>, Ni<sup>2+</sup>, Ag<sup>+</sup> and Hg<sup>2+</sup> complexes with PAMAM, **L** and with the EDTA and PDTA tetraamides **L**<sup>1</sup> were determined by pH-metric methods using ligand concentrations of 1 × 10<sup>-3</sup> (PAMAM) and 2 × 10<sup>-3</sup> mol·dm<sup>-3</sup>, a metal to ligand ratio of 1:1 and 1:2 in all cases and the data were analysed by SUPERQUAD [9] and HYPERQUAD 2000 [10]. The standard deviations quoted refer to random errors. UV–Vis spectra were obtained on a Helios α Thermo Spectronic spectrophotometer in the region of 200–800 nm, pH 4–10.8, [M<sup>2+</sup>] = [**L** or **L**<sup>1</sup>(a)] = 2 mM, where M<sup>2+</sup> is Cu<sup>2+</sup> or Ni<sup>2+</sup>, **L** = PAMAM dendrimer and **L**<sup>1</sup>(a) is EDTA amide (R = H, R' = H).

### 2.3. <sup>1</sup>H NMR titrations

<sup>1</sup>H NMR spectra for **L**<sup>1</sup> (b), **L**<sup>1</sup>(b)–Hg(II), PAMAM–Ag(I) and PAMAM–Hg(II) systems were recorded in D<sub>2</sub>O, on a Bruker Avance DPX 400 FT spectrometer; the ligand concentration was 2 × 10<sup>-3</sup> mol·dm<sup>-3</sup>, and ligand to metal ratios were 1:1 and 1:2. TSP, sodium (3-trimethylsilyl)-2,2,3,3-tetradeteriopropanoate, was used as internal <sup>1</sup>H standard. The pD of the samples was regulated using small volumes of concentrated HNO<sub>3</sub> in D<sub>2</sub>O or NaOD solutions and converted into pH using equation pH = 0.936pD + 0.41 [11].

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